IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Sackstein		
SERIAL NUMBER:	10/042,421	EXAMINER:	Gambel, Phillip
FILING DATE:	October 18, 2001	ART UNIT:	1644
FOR:	HEMATOPOIETIC CELL E-SELECTIN/ L-SELECTIN LIGAND POLYPEPTIDES AND METHODS OF USE THEREOF		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

In reply to the Office Action mailed August 20, 2009 (hereinafter "the Office Action"), Applicant requests a Pre-Appeal Brief Conference for Review and submit the following Remarks. This paper is timely filed if submitted on or before on November 20, 2009. Applicant believes no additional fees are due. However, the Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. **50-0311**, Reference No. **36459-501001US**.

Remarks start on page 2 of this paper.

REMARKS

The claims are directed to highly purified preparations of glycosylated polypeptides comprising a CD44 amino acid backbone and sialylated, fucosylated glycans and having E-selectin or L-selectin ligand activity.

The examiner maintains a series of rejections under 35 U.S.C. § 103(a) citing Sackstein 1997[1/], Stamenkovic[2/], and Dougherty[3/] as primary references. The secondary references cited by the examiner include Ni[4/], McEver[5/], Lasky,[6/] and Oxley.[7/] These rejections, however, fail to provide a reasonable rationale or clear articulation as to how a person of ordinary skill in the art could have arrived at the claimed invention based on the teaching of these references. MPEP § 2142 summarizes the law on this point as follows (citations omitted):

> The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

The rejections set forth by the examiner have failed to meet this standard and should be withdrawn. A full analysis of Sackstein 1997, Stamenkovic, Dougherty, Ni, and McEver can be found on pages 16-29 of the Appeal Brief filed February 20, 2009. Lasky and Oxley are cited in new grounds of rejection in the Office Action of August 20, 2009 and will be addressed hereinafter. It should be noted that none of these references disclose highly purified preparations of the CD44 glycoproteins according to the present claims. Rather, it is the examiner's position that the cited references provide "for key starting materials (e.g., KG1a, Namalwa), probes to isolate CD44, CD44R1 and HCELL (e.g., L-selectin ligand probes or CD44 probes) as well as functional and structural characteristics for said molecules" in order to isolate the recited highly purified preparations of CD44 glycoproteins.[8/] The analysis provided herein will demonstrate

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1/ Sackstein *et al.*, Blood. 1997 Apr 15;89(8):2773-81.
2/ Stamenkovic *et al.*, EMBO J. 1991 Feb;10(2):343-8.
3/ Dougherty *et al.*, J Exp Med. 1991 Jul 1;174(1):1-5.
4/ U.S. Patent No. 5,942,417.
5/ U.S. Patent No. 6,124,267.
6/ U.S. Patent No. 5,652,343.
7/ Oxley *et al.*, Blood. 1994 Nov 15;84(10):3299-306.
8/ Page 4, fifth full paragraph, of the Office Action mailed August 20, 2009.

that combining prior art elements according to examiner could not predictably yield highly purified preparations of CD44 glycoproteins.

Sackstein 1997 discloses the identification of an activity of an unknown protein contained within the whole cell lysates of KG1a cells. Sackstein 1997 fails to identify the polypeptide as having a CD44 amino acid backbone, let alone purify a CD44 glycoform. Applicant has submitted evidence demonstrating that one of ordinary skill in the art would not have predicted CD44 to be the molecule described by Sackstein 1997. This line of evidence and rationale has not been properly considered by the examiner and is not discussed in the Office Action. For example, Sackstein 1997, in the Abstract, specifically states that the "native membrane L-selectin ligand exhibit[s] sulfate-independent function." Maiti[9/] teaches that the activity of CD44 was thought to require sulfation, and accordingly a person of ordinary skill in the art would have been led to believe that the molecule described by Sackstein 1997 was not CD44. This point is bolstered by the Picker Declaration of record. This evidence has not been properly considered.

The same is true with regard to the rejections in view of Stamenkovic and Dougherty. Neither Stamenkovic nor Dougherty, however, identify specific glycoforms of CD44 or distinguish functional differences between CD44 glycoforms, and accordingly, could not lead one of ordinary skill in the art to a purified preparation containing CD44 glycoforms comprising sialylated, fucosylated glycans. Applicant has submitted evidence demonstrating that one of skill in the art would not have been able to predictably modify the teachings of these references. Namely, Katoh[10/] showed that the adhesive function of CD44 to its well-known ligand hyaluronic acid is actually inhibited by certain carbohydrate modifications, such as sialic acid. Thus, a CD44 glycoform comprising sialylated glycans would have not been thought to possess any adhesion specificity, let alone be identified as an E- or L- selectin ligand. The teachings of Picker,[11/] Berg,[12/] Jutila,[13/] and Walcheck[14/] each, and altogether, provide evidence for the well-established (prior) canon in the art — that is, it was generally understood in the art at the time of invention that CD44 was not a selectin ligand. This evidence has not been properly considered by the examiner.

9/ Maiti *et al.*, Science. 1998 Oct 30;282(5390):941-3.
10/ Katoh *et al.*, J Exp Med. 1995 Aug 1;182(2):419-29.
11/ Picker *et al.*, American Journal of Pathology, 136:1053-1068, 1990.
12/ Berg *et al.*, J Exp Med. 1991;174:1461-1466.
13/ Jutila *et al.*, J Immunol. 1994;153:3917-3928
14/ Walcheck *et al.*, J Exp Med. 1993 Sep 1;178(3):853-63.

The inappropriateness of Namalwa cells disclosed in Stamenkovic was previously addressed in the Response to Office Action submitted Sept. 27, 2004 (pp. 20-21) and in the Response to Final Office Action (pp. 17-18) and accompanied Declaration of Robert Sackstein submitted July 27, 2005. As explained in the above, it would not be possible for a skilled artisan to produce the highly purified preparations of the recited CD44 glycoforms using the Namalwa cells because these cells lack the necessary glycosyltransferases to produce the recited CD44 glycoforms. This evidence has never been specifically refuted or addressed by the examiner and has not been properly considered by the examiner.

As a result, there is no clear articulation on record as to how a skilled artisan would have modified the teaching of Sackstein 1997, Stamenkovic, and/or Dougherty to arrive at the claimed purification. Rather, the examiner, improperly, sustains the rejections with the mere conclusory statement that the submitted evidence "appear to ignore the relationship of the references molecules to a human hemopoietic cell line."[15/]

Instead of articulating any clear rationale as to how a person of ordinary skill in the art would have been led to defining a specialized glycoform of CD44 as a selectin ligand, the examiner relies on newly cited references of Lasky and Oxley. The examiner relies on Lasky for its teaching of an L-selectin-IgG chimeric molecule and concludes that "[w]hile applicant focuses on … Sackstein's (1997) lack of teaching of a CD44 glycoform …, Sackstein 1997 clearly [teaches] the identification of a glycoprotein L-selectin ligand expressed on the human hemopoietic cell line KG1a, wherein the L-selectin ligand does *not contain MECA antibody-specific epitopes and is not dependent on sulfation*."[16/] The examiner alleges on page 8 of the Office Action that the teachings of Sackstein 1997 may be modified by using the L-selectin-IgG of Lasky, which may be used to purify the CD44 glycoform of the present claims. This conclusion, however, ignores the teachings of Lasky and ignores the evidence of record. First, Lasky clearly uses the L-selectin-IgG to obtain *MECA-79 reactive antigen that is sulfated.*[17/] Thus, the examiner has not articulated how a "probe" used to identify sulfated, *MECA-79 reactive antigens* could be predictably used to obtain the L-selectin ligand of Sackstein 1997 that does *not contain MECA-79 antibody-specific epitopes and is not dependent on sulfation.* The examiner's own rationale is inconsistent, not reasonable, and not clearly articulated.

15/ Office Action page 4, last paragraph.

16/ Office Action at page 7, last paragraph (emphasis added).

17/ See Lasky at column 4, lines 46 - 65 (Summary of the Invention)(stating that "L-selectin-IgG chimera to precipitate inorganic sulfate-labeled material" which was "abolished by treatment of the sulfate-labeled proteins with sialidase" and, further, that the "monoclonal antibody, termed MECA-79,…precipitated both components.").

Further, the examiner's conclusion assumes that L-selectin-IgG binds to the recited glycoforms of CD44 and assumes that KG1a cells express a single L-selectin ligand, thereby ignoring the evidence of record. The examiner has not shown that the L-selectin-IgG binds to the recited CD44 glycoforms. Even assuming, *arguendo,* L-selectin-IgG binds to the recited CD44 glycoforms,[18/] evidence of record (Sackstein 2000; IDS December 8, 2003, #AX), clearly provides that KG1a cells express at least one other L-selectin ligand, *i.e.,* PSGL-1.[19/] Indeed, evidence of record (Spertini; IDS December 8, 2003, #AAA) provide direct evidence that L-selectin-Ig identifies PSGL-1.[20/] Accordingly, use of the L-selectin-IgG could not produce the recited highly purified preparations of the CD44 glycoproteins because the L-selectin-IgG would not selectively bind to CD44 glycoproteins. Any attempts to purify cell lysates with L-selectin-IgG could not possibly result in a preparation comprising less than 5% of a polypeptide other than the recited glycosylated CD44 polypeptide. There is no rationale provided by the examiner that would lead to a contrary conclusion.

The examiner also relies on Oxley for its teaching of a distinct L-selectin ligand that is expressed by KG1a cells. This reference, however, merely demonstrates that the distinct L-selectin ligand expressed by KG1a cells is not CD34 (i.e., that it is distinct from CD34, a molecule identified by Lasky to serve as an L-selectin ligand). Accordingly, the reference represents a failure to identify and purify a distinct L-selectin ligand expressed by KG1a cells. There is no rationale provided by the examiner that would suggest that the negative results (i.e., not CD34) of Oxley would lead a person of ordinary skill in the art to the claimed subject matter.

In view of the above, Applicant respectfully submits that the examiner (1) has failed to clearly articulate a rationale for supporting any of the rejections set forth under 35 U.S.C. 103; (2) has set forth an inconsistent and flawed rationale; and (3) has not properly considered the evidence supporting non-obviousness of the claimed subject matter, including prior Responses to Office Actions and Declarations. An indication of allowance of all claims is solicited.

Respectfully submitted,

Dated: August 26, 2009

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18/ Applicant does not concede that L-selectin-IgG binds to the recited CD44 glycoforms.

19/ Sackstein *et al.*, Blood. 2000 96: 2765-2774. See *e.g.*, Figure 2 showing the expression of PSGL-1 cells on KG1a cells.

20/ Spertini *et al.*, J Cell Biol. 1996 Oct;135(2):523-31.